UNITED STATES DISTRICT COURT
DISTRICT OF CONNECTICUT

STATE OF CONNECTICUT,	:	CIVIL ACTION NO.
ATTORNEY GENERAL	:	
RICHARD BLUMENTHAL	:	
Plaintiff,	:	
	:	
v.	:	
	:	
UNITED STATES FOOD	:	
AND DRUG ADMINISTRATION	:	
Defendant.	:	MARCH 31, 2008

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION

1. Plaintiff brings this action pursuant to the Food, Drug, and Cosmetic Act (the "Act"), 21 U.S.C. §§ 301-394, and the Administrative Procedure Act (APA), 5 U.S.C. §§ 702 and 706, to compel the United States Food and Drug Administration (FDA) to act on the petition of Richard Blumenthal, the Attorney General for the State of Connecticut dated January 23, 2004, as supplemented on March 16, 2005 ("Petition"), requesting that the FDA require Purdue Pharma L.P. ("PPLP") to take various actions to expressly warn physicians and patients of the increased occurrence of side effects or potentially serious adverse reactions resulting from prescribing OxyContin at dosing intervals more frequent than the manufacturer's FDA approved dosing schedule. Specifically, in his Petition, Attorney General Blumenthal requested that the FDA require PPLP to (i) revise OxyContin's black box warning to expressly reinforce the FDA approved dosing regimen and to add specific information regarding the potential dangers associated with an off-label dosing schedule; (ii) strengthen the warning and safety labeling concerning the

dosing concerns; and (iii) issue a "Dear Healthcare Professional" Letter to inform all prescribers of controlled substances about the potential risks of prescribing OxyContin at dosing intervals that are shorter than the manufacturer's recommended 12-hour dosing schedule. In addition or as an alternative to the above, the Attorney General requested that the FDA disseminate warnings concerning the OxyContin dosing issues through a Safety Alert, Public Health Advisory, Talk Paper or Urgent Notice.

Although more than four years have passed since the Attorney General initially filed his Petition, FDA has neither granted nor denied the Petition, nor has the FDA taken any action to adequately warn physicians and their patients about the risks associated with prescribing OxyContin at dosing intervals that are shorter than the manufacturer's recommended dosing schedule.

The Attorney General's central purpose in filing the Petition was to ensure complete and accurate disclosure to prescribers of all material information relating to the prescribing of OxyContin so that treatment decisions reflect full knowledge of the risks and benefits posed by prescribing OxyContin. Therefore, to protect patient health by preventing needless injury, and to protect public safety by limiting diversion of OxyContin, Attorney General Blumenthal seeks a declaration that the FDA has acted unlawfully by withholding action on the Attorney General's Petition and an order requiring the FDA to act thereon.

PARTIES

2. Plaintiff Richard Blumenthal is the Attorney General for the State of Connecticut. He brings this action so that the FDA will be required to respond to his Petition, which he

filed pursuant to 21 C.F.R. §10.30 to address issues that have the potential to negatively impact the interests of public health and public safety.

3. The United States Department of Health and Human Services (HHS) is an agency of the federal government, and the defendant FDA is an agency within HHS. By delegation from HHS, the FDA is responsible for the administration of the Act, 21 U.S.C. §301 et seq. See 21 C.F.R. §5.10. In particular, the FDA regulates the content and format of prescription drug labeling. 21 C.F.R. §201. As set forth in more detail below, the FDA has violated the law by failing to act on the Attorney General's Petition seeking adequate labeling on OxyContin to inform the prescribers and patients about the risks of prescribing OxyContin for intervals that are shorter than the manufacturer's recommended dosing schedule.

JURISDICTION

4. This Court has jurisdiction pursuant to 28 U.S.C. §1331.

FACTS

5. The primary objective of the Act is the protection of public health through the regulation of certain medical products moving in interstate commerce. The Act vests the FDA with the regulatory authority and responsibility for ensuring the safety of all marketed medical products, and it prohibits the introduction into interstate commerce of any drug that is misbranded. 21 U.S.C. §331(a).

6. OxyContin is a drug within the meaning of the Act, 21 U.S.C.A. §321(g), and a new drug within the meaning of 21 U.S.C. §321(p).

7. Pursuant to the statutory scheme, a drug shall be deemed misbranded if its labeling is false or misleading in any particular. In determining whether a drug's

labeling is misleading, the FDA shall take into account, among other things, "not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling … fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use of the article to which the labeling … relates under the conditions of use prescribed in the labeling … thereof or under such conditions of use as are customary or usual." 21 U.S.C. §321(n). A drug is also considered misbranded unless its labeling bears adequate warnings. 21 U.S.C. §352(f).

8. OxyContin is a controlled-release opioid that was designed to deliver a consistent level of oxycodone over a twelve hour period. The drug's patented delivery system is constructed scientifically for twelve hour or biphasic absorption, meaning that each dose would be eliminated from the patient's system within 12 hours of taking the dose.

9 OxyContin's package insert contains cautionary language advising prescribers to be especially vigilant when prescribing the highest dosage levels, 80 mg and 160 mg doses, to patients not previously exposed to opioids as these strengths could cause fatal respiratory depression. Further, the insert advises that the risks are elevated for patients in certain populations (e.g., elderly (over 65) and patients with kidney or liver impairment) whose ability to eliminate the drug from their systems might be compromised.

10. The manufacturer's FDA approved dosing schedule calls for dosing intervals of 12 hours ("q12h"). Consistent with this dosing schedule, the OxyContin package insert refers on 29 separate occasions to information that supports dosing intervals of q12h. All of the information in the package insert relating to the rate of absorption of OxyContin

into the blood and the corresponding side effect profiles are based on a q12h dosing principle.

11. Equally important, as stated in the Petition, PPLP's internal documents indicate that "100% of patients in clinical trials were dosed at q12h" and OxyContin's package insert states "[t]here is no clinical information on dosing intervals shorter than q12h."

12. All of the PPLP recommended prescribing guidelines for OxyContin, safety information and the FDA approval for marketing are based on q12h dosing. As the Director of the FDA's Controlled Substance Staff stated when discussing OxyContin's q12h dosing principle, "the safety of the drug is based on taking the drug exactly as intended."

13. Notwithstanding the information contained in the package insert concerning OxyContin's q12h dosing regimen and the FDA Director's admonition, the Petition points to significant evidence that many physicians customarily prescribed OxyContin at dosing intervals more frequent than the recommended q12h, to the point that at the time the Petition was submitted to the FDA in 2004, approximately twenty percent (20%) of all prescriptions were written for q8h or more frequently. This is at least in part due to what PPLP acknowledged internally as a fundamental misunderstanding by healthcare providers of how to prescribe OxyContin given its unique controlled-release delivery system which differs from the delivery systems of most other opioids.

14. Moreover, the Petition describes significant evidence developed by PPLP indicating that dosing frequencies shorter than q12h may increase the risks of side effects in patients. Specifically, PPLP developed evidence demonstrating that a dosing frequency of q8h "will increase the blood levels thereby increasing the risk of side effects

such as euphoria and sedation" which, among other things, would increase the risk of addiction or respiratory depression. PPLP's failures to disclose this information to prescribers in the face of the company's knowledge that it is customary for physicians to prescribe the drug using the off-label dosing regimen renders the label misleading and misbranded pursuant to the Act.

15. In light of the uniqueness of the OxyContin controlled release delivery system, physicians' misunderstanding of the system and the dearth of publicly available clinical information concerning dosing intervals that are shorter than q12h, many providers prescribing OxyContin at shorter intervals are unwittingly leading their patients into the risk of increased side effects to be expected at such dosing levels.

16. Certain patients receiving OxyContin at intervals more frequent than q12h are more at risk of developing side effects and potentially serious adverse drug reactions due to the pharmacologic action of the drug. When a physician prescribes at q8h a drug that is designed to release its active ingredient over a 12 hour period, there is an overlapping period of time when two doses are affecting the patient at once. This increases the risks of harmful side effects and serious adverse events, such as hypoxia or respiratory arrest, and increases the potential for addiction. These risks are heightened for those patients whose ability to eliminate the drug from their systems is compromised due to age, gender or disease.

17. The public health and safety risks associated with an increase in the frequency of OxyContin's dosing is well documented in the Petition. The FDA's postmarketing drug surveillance program ("MEDWATCH") compiles adverse event reports submitted to the FDA. MEDWATCH reports are, by definition, deemed to be of a serious nature. For the

period from 1999 to 2003 (the time period covered by the Petition) when OxyContin was listed as a suspect medication, 49 separate adverse events were reported where death was the outcome. Each of these 49 reports indicate that the decedent was prescribed OxyContin at least q8h or more frequently. In 12 of those cases, OxyContin was identified as likely being one of the primary causes of death.

18. Moreover, for the period from 1999 to 2003, the FDA received 247 serious adverse event reports where the event was non-fatal and the patient was prescribed OxyContin at least q8h or more frequently. In those reports, 52 cases were identified where OxyContin was identified as a suspect cause of the event and which resulted in a life-threatening event, hospitalization or some other medically significant outcome. Many of these events included addiction and/or withdrawal symptoms, dizziness, myoclonic jerks, nausea, somnolence and respiratory depression. The side effects often developed shortly after a patient's dosing schedule was increased to q8h (or more frequently), and they subsided or disappeared altogether when either the dose was reduced or the time interval between doses was increased, indicating a strong correlation between the off-label dosing and the onset of an adverse event.

19. When comparing the percentage of non-fatal adverse event reports associated with an off-label dosing regimen of q8h or more frequently to the overall percentage of OxyContin prescriptions with an off-label dosing regimen of q8h or more frequently, the comparison suggests that this off-label dosing regimen is accompanied by a significantly higher risk of experiencing adverse events. In 1999, PPLP's own data indicates that 12.1% of the OxyContin prescriptions were written q8h or more frequently, yet they accounted for 35% of the MEDWATCH OxyContin adverse event reports for that year.

In 2000, PPLP's data indicates that 14% of the OxyContin prescriptions were written q8h or more frequently, yet they accounted for 22% of the OxyContin adverse event reports. In 2001, PPLP's data indicates that 20.2% of the OxyContin prescriptions were written q8h or more frequently, yet they accounted for 37% of the OxyContin adverse event reports. In 2002, PPLP's data indicates that 18% of the OxyContin prescriptions were written q8h or more frequently, yet they also accounted for 36% of the OxyContin adverse event reports. This pattern illuminates the strong correlation between prescribing off-label for q8h or more frequently and the increased incidence of adverse events.

20. The increase in the number of doses beyond the recommended q12h also increases the potential for diversion of the drug for illicit use, an obviously serious public health and safety risk. The Petition specifically points to PPLP's internal concerns that q8h or more frequent prescribing may lead to diversion of the drug. PPLP's internal documents acknowledge that shorter dosing intervals essentially provide the patient with an "extra dose" per day which "may be an opportunity for diversion," contributing to an illicit supply of OxyContin.

21. The flow of diverted OxyContin into Connecticut continues unabated to this day. The United States Department of Justice's "National Drug Threat Assessment 2008" notes that "[t]he distribution and abuse . . . of prescription narcotics such as OxyContin . . . pose the greatest drug threats in the NE region."

PROCEDURAL HISTORY

22. On January 23, 2004, in light of the significant increased public health and safety risks associated with prescribing OxyContin more frequently than q12h, the Attorney General filed his Petition, attached hereto as **Exhibit A** (without attachments). The

Petition was initially filed in redacted form due to PPLP's claims of confidentiality with respect to certain documents it had produced.

23. On July 21, 2004, the FDA provided the Attorney General with a preliminary response in writing, attached hereto as **Exhibit B**, indicating that the FDA was unable at that time to reach a decision because the Petition "raises significant and complex issues requiring extensive review and analysis . . . ."

24. On January 26, 2005, the Attorney General supplemented his Petition by providing it in unredacted form in response to the FDA's indication of its willingness to accept the unredacted version. In his January 26 correspondence, attached hereto as **Exhibit C** (without attachments), the Attorney General indicated that his submission of the unredacted Petition was necessary in light of the FDA's substantial delay in acting on the Petition and the continuing significant health risks at stake in light of that delay, and to ensure that the record was full, complete and accurate for consideration by the FDA.

25. On February 10, 2005, the FDA provided the Attorney General with a response in writing, attached hereto as **Exhibit D**, returning the unredacted Petition to the Attorney General notwithstanding its earlier stated willingness to accept it. In light of its desire to "obtain[] any information that bears on the safety of the product [it] regulate[s]," however, the FDA invited the Attorney General to submit the same unredacted Petition to the FDA's Acting Deputy Director, Center for Drug Evaluation and Research.

26. On March 16, 2005, the Attorney General submitted the unredacted version of the Petition, attached hereto as **Exhibit E**.

27. On September 28, 2006, having received no response from the FDA with respect to the Petition, the Attorney General submitted a request in writing, attached hereto as

Exhibit F, seeking clarification as to when the FDA intended to rule on the issues raised in the petition.

28. On July 27, 2007, still having received no response from the FDA with respect to the Petition or to his September 28, 2006 correspondence, the Attorney General again submitted a request in writing, attached hereto as **Exhibit G**, urging the FDA to issue its formal decision on the Petition and to order the label warnings as quickly as possible.

29. On September 14, 2007, the FDA responded to the Attorney General's July 27 correspondence indicating that it was actively working on a response to the Attorney General's Petition, noting that it was not able to provide a timeframe for a ruling on the Petition and that it has not reached any preliminary decision or conclusion with respect to the issues raised in the Petition. See **Exhibit H** attached hereto.

30. The Attorney General's Petition provides sufficient grounds for the FDA to (i) revise the black box label to expressly warn prescribers about the approved dosing regimen and to highlight the increased risks attendant to an off-label dosing regimen; (ii) strengthen the warning and safety labeling concerning the off-label dosing regimen; and (iii) require a "Dear Healthcare Professional" Letter to inform all prescribers of controlled substances about the potential risks of prescribing OxyContin at dosing intervals that are shorter than the manufacturer's recommended dosing schedule, pursuant to 21 C.F.R. §201.57 and 21 C.F.R. §200.5.

31. To date -- *after more than four years* -- the FDA has yet to issue a decision on the Attorney General's Petition, nor has it taken action subsequent to the Petition to require adequate warnings of the substantial risks associated with prescribing OxyContin at a dosing frequency more frequent than q12h. Specifically, the FDA has (i) *failed* to require

a black-box warning addressing this issue, (ii) *failed* to strengthen the warning and safety labeling concerning the dosing concerns, or (iii) *failed* to require PPLP to disseminate a "Dear Healthcare Professional" letter or other communications to warn the healthcare community about the risks. The FDA has simply and utterly failed to take *any* such action despite the MEDWATCH program's receipt of information supporting the concerns raised in the Petition and reiterated in this Complaint.

32. The considerable danger to public health and safety occasioned by the FDA's nonaction counsels in favor of expeditious action on the Attorney General's Petition. The pace of the FDA's decisional process is lagging unreasonably in light of the nature and extent of the public health and safety interests prejudiced by the FDA's delay. Without FDA action on the Attorney General's Petition to add heightened warnings to the label of OxyContin, patients prescribed OxyContin will continue to be exposed to the potential for injury posed by the off-label OxyContin dosing regimen. With sufficient warnings and information, the FDA could significantly mitigate the prospect of unnecessary and potentially serious adverse events.

33. Likewise, without FDA action on the Attorney General's Petition, diversion of OxyContin, affected to some degree by the off-label dosing regimen, will continue to pose a threat to the public's safety in Connecticut and elsewhere.

CLAIMS FOR RELIEF

1. The FDA's failure to act on the Attorney General's Petition constitutes agency action unlawfully withheld or unreasonably delayed and violates the Administrative Procedure Act, 5 U.S.C. § 706(1).

2. The FDA's failure to act on the Attorney General's Petition is not in accordance with law and violates the Administrative Procedure Act, 5 U.S.C. § 706(2)(A).

WHEREFORE, Plaintiff requests that this Court:

A. Declare unlawful FDA's failure to act on the Attorney General's Petition;

B. Order the FDA to issue a decision on the Attorney General's Petition within 30 days of declaring FDA's failure to act unlawful;

C. Award the Attorney General his reasonable costs and attorney's fees under 28 U.S.C. § 2412; and

D. Grant all other appropriate relief.

Respectfully submitted,

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